Synthesis, Monoamine Transporter Binding, Properties, and Functional Monoamine Uptake Activity of 3*β*-[4-Methylphenyl and 4-Chlorophenyl]-2*β*-[5-(Substituted phenyl)thiazol-2-yl]tropanes

Paul K. Gong,[†] Bruce E. Blough,[†] Lawrence E. Brieaddy,[†] Xiaodong Huang,[†] Michael J. Kuhar,[‡] Hernán A. Navarro,[†] and F. Ivy Carroll*,[†]

Center for Organic and Medicinal Chemistry, Research Triangle Institute, Research Triangle Park, North Carolina 27709-2194, and Yerkes National Primate Center of Emory University, 954 Gatewood Road NE, Atlanta, Georgia 30329

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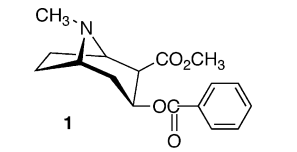
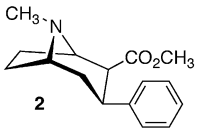
Synthetic methods were developed for the synthesis of the 3*β*-(4-substituted phenyl)-2*β*-[5-(substituted phenyl)thiazol-2-yl]tropanes (**4a**−**s**). The compounds were evaluated for their monoamine transporter binding and monoamine uptake inhibition properties using both rat brain tissue and cloned transporter assays. In general, the compounds showed higher dopamine transporter (DAT) affinity relative to the serotonin and norepinephrine transporters (SERT and NET, respectively) and greater [^{3}H]dopamine uptake inhibition potency relative to [^{3}H]serotonin and [^{3}H]norepinephrine uptake inhibition. Several compounds were DAT selective relative to the SERT and NET in the monoamine transporter binding assays. The most potent and selective analog in the functional monoamine uptake inhibition test was 3*β*-(4-methylphenyl-2*β*-[5-(3-nitrophenyl)-thiazol-2-yl]tropane (**4p**).

The neurotransmitter dopamine (DA[a]) is involved in vital functions such as locomotion, feeding, emotion, and reward.[1] Compounds that inhibit binding to the DA transporter (DAT) and, thus, block reuptake of DA have been studied as potential drugs to treat Parkinson's disease,[2−4] attention deficit hyperactivity disorder (ADHD),[5,6] depression,[7] obesity,[8] and cocaine (**1**) addiction.[9] One of the most studied classes of DA uptake inhibitors is the 3-phenyltropanes.[10−14] The lead DA uptake inhibitor in this class was 3*β*-phenyltropane-2*β*-carboxylic acid methyl ester (**2**, WIN 35,065-2).[15,16] Many WIN 35,065-2 analogs have been synthesized and evaluated for their binding to the DAT.[10−14] Replacement of the 2*β*-carbomethoxy group with certain heterocyclic groups led to analogues that retained high affinity for the DAT and, in some cases, were DAT selective relative to binding at the serotonin and norepinephrine transporters (SERT and NET, respectively).[17−19] One of the most interesting compounds is the DAT selective inhibitor 3*β*-(4-chlorophenyl)-2*β*-[3-(4-methylphenyl)isoxazol-5-yl]tropane (**3**, RTI-336), which is in advanced preclinical development.[17,20−22] Another class of DAT selective 2*β*-heterocyclic analogues discovered in the initial study of 3*β*-(aryl)-2*β*-heterocyclic tropanes was 3*β*-(4-chlorophenyl)-2*β*-(5-phenylthiazol-2-yl)-tropane (**4a**, RTI-219).[19] In this paper, we describe the synthesis of a number of new 3*β*-(4-chloro and 4-methylphenyl)-2*β*-[5-(substituted phenyl)thiazol-2-yl]tropanes (**4b**−**s**) and report their monoamine transporter binding properties and their functional monoamine uptake inhibition activity.



1



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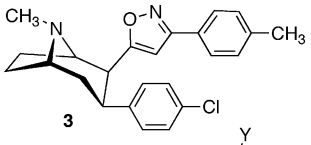

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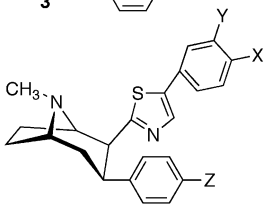

4a, X = Y = H, Z = Cl
4b, X = F, Y = H, Z = Cl
4c, X = Cl, Y = H, Z = Cl
4d, X = Br, Y = H, Z = Cl
4e, X = H, Y = Br, Z = Cl
4f, X = NO_2, Y = H, Z = Cl
4g, X = H, Y = NO_2, Z = Cl
4h, X = CH_3O, Y = H, Z = Cl
4i, X = Y = Cl, Z = Cl
4j, X = Y = CH_3O, Z = Cl
4k, X = F, Y = H, Z = CH_3
4l, X = Cl, Y = H, Z = CH_3
4m, X = Br, Y = H, Z = CH_3
4n, X = H, Y = Br, Z = CH_3
4o, X = NO_2, Y = H, Z = CH_3
4p, X = H, Y = NO_2, Z = CH_3
4q, X = CH_3O, Y = H, Z = CH_3
4r, X = Y = Cl, Z = CH_3
4s, X = Y = CH_3O, Z = CH_3

Chemistry

The 4-substituted phenylthiazole analogues **4b**−**d**, **4f**, **4h**, and **4m** were synthesized using a procedure exactly analogous to

* To whom correspondence should be addressed. Dr. F. Ivy Carroll, Organic and Medicinal Chemistry, Research Triangle Institute, Post Office Box 12194, Research Triangle Park, NC 27709-2194, Telephone: 919 541-6679. Fax: 919 541-8868. E-mail: fic@rti.org.

† Research Triangle Institute.

‡ Yerkes National Primate Center of Emory University.

[a] Abbreviations: DAT, dopamine transporter; SERT, serotonin transporter; NET, norepinephrine transporter; DA, dopamine; 5HT, serotonin; NE, norepinephrine; EDCI, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; HOAt, 1-hydroxy-7-azabenzotriazole; HEK, human embryonic kidney.

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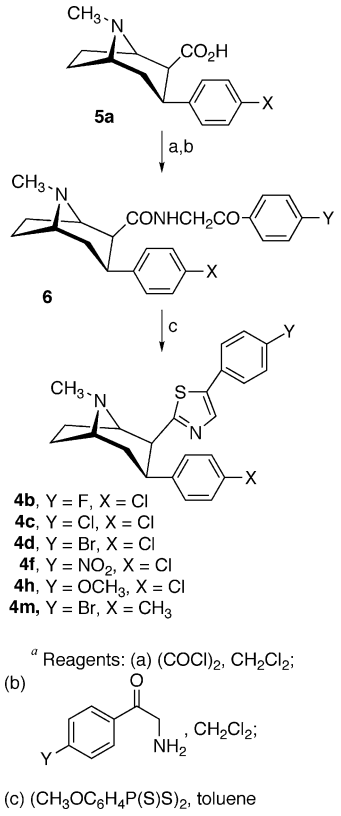
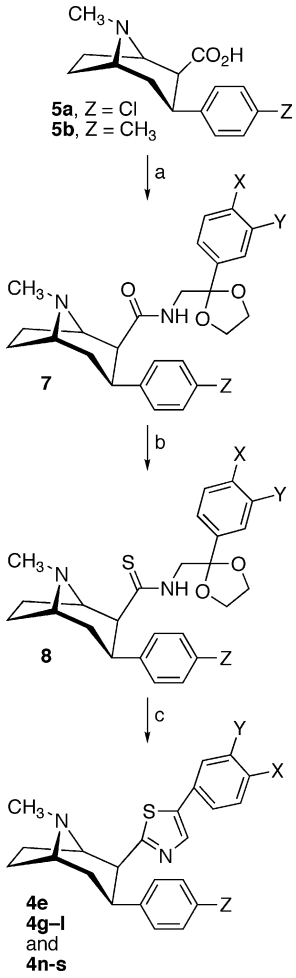
Scheme 1



[a] Reagents: (a) $(COCl)_2$, CH_2Cl_2;

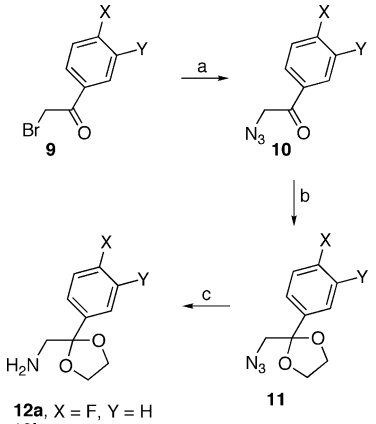
that used to prepare **4a** (Scheme 1).[19] The acid **5a** was treated with oxalyl chloride, and the resultant acid chloride was condensed with the appropriate 2-aminoacetophenone to give the amides **6**. Cyclization with Lawesson's reagent gave the 3*β*-(4-chlorophenyl)-2*β*-[5-(substituted phenyl)thiazol-2-yl]tropanes (**4b**−**d**, **4f**, **4h**, and **4m**). Because the yields obtained by this procedure were low when attempted for the 3*β*-(4-methylphenyl)-2*β*-[5-(substituted phenyl)thiazol-2-yl]tropane analogs, a new procedure outlined in Scheme 2 was developed. Coupling of **5a** or **5b** with the appropriately protected aminoacetophenones (**12a**−**h**) using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and 1-hydroxy-7-azabenzotriazole (HOAt) in dimethylformamide afforded the amides (**7**). Treatment of amides **7** with cold triflic anhydride in the presence of pyridine formed an intermediate imino triflate that, when subjected to an excess of hydrogen sulfide gas, yielded the thioamides **8**.[23] The thioamides **8** were cyclized to the desired **4e**, **4g**−**l** and **4n**−**s** by briefly heating in concentrated hydrochloric acid. The protected aminoacetophenones **12a**−**h** needed to synthesize the amides **7** were produced in a three-step synthesis from commercially available phenacyl bromides **9a**−**h**, as outlined in Scheme 3. Heating a solution of **9a**−**h** in dimethylsulfoxide with sodium azide provided the phenacyl azides **10a**−**h**. Treatment of **10a**−**h** with ethylene glycol in chloroform using boron trifluoride etherate as the acid catalyst yielded the ketone-protected phenacyl azides **11a**−**h**. Reduction of the azides **11a**−**h** to the protected 2-aminoacetophenones **12a**−**h** was achieved by first converting the azides **11a**−**h** to the phosphazo intermediate with triphenylphosphine followed by treatment with water (Staudinger reaction[24]).

Scheme 2[a]



[a] Reagents and conditions: (a) **12a**−**h**, EDCl, HOAt, DMF; (b) (i) Tf_2O, pyridine, CH_2Cl_2, −45 to 0 °C, 4 h; (ii) H_2S(g), 0 °C, 1 h; (c) (i) 12 N HCl, 60 °C, 30 min; (ii) 3 M NaOH.

Scheme 3[a]

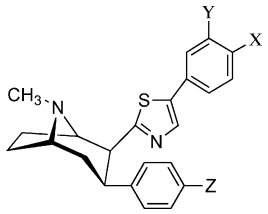


[a] Reagents and conditions: (a) NaN_3, DMSO; (b) $HOCH_2CH_2OH$, $BF_3{\cdot}Et_2O$, $CHCl_3$; (c) (i) PPh_3, THF; (ii) H_2O.

Biological Section

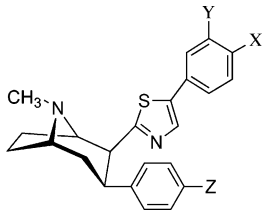
Target compounds were evaluated in two different monoamine transporter binding assays. In one assay, the striata, midbrain, or frontal cortex of male Sprague−Dawley rats (200−250 g) were used for competition binding assays at the DAT, SERT, and NET.[25,26] The final concentration of radioligands in the assays was 0.5 nM [^{3}H]WIN 35,065−2 for the DAT, 0.2 nM

Table 1. Monoamine Transporter Binding Properties of 2-Phenylthiazole Analogs Using Rat Brain Tissues



cmpd	Z	X	Y	DAT, IC_{50} (nM) [^{3}H]WIN35,428	SERT, K_i (nM) [^{3}H]Paroxetine	NET, K_i (nM) [^{3}H]Nisoxetine
WIN 35,065-2				23	1900	920
4a	Cl	H	H	5.7	>2000	8560
4b	Cl	4F	H	6 ± 1	371 ± 70	>2000
4c	Cl	4Cl	H	20 ± 3	903 ± 320	>2000
4d	Cl	4Br	H	107 ± 20	840 ± 20	>2000
4e	Cl	H	Br	18 ± 6	280 ± 20	>2000
4f	Cl	NO_2	H	20 ± 3	980 ± 100	>2000
4g	Cl	H	NO_2	5 ± 1	301 ± 30	>2000
4h	Cl	CH_3O	H	14 ± 3	800 ± 100	>2000
4i	Cl	Cl	Cl	440 ± 100	380 ± 30	>2000
4j	Cl	CH_3O	CH_3O	65 ± 6	1510 ± 80	>2000
4k	CH_3	F	H	12 ± 4	2240 ± 600	>2000
4l	CH_3	Cl	H	22 ± 3	1110 ± 70	>2000
4n	CH_3	H	Br	10 ± 2	312 ± 10	>2000
4o	CH_3	NO_2	H	41 ± 5	1690 ± 240	>2000
4p	CH_3	H	NO_2	4 ± 1	10,000	>4300
4q	CH_3	CH_3O	H	15 ± 6	>2000	>2000
4r	CH_3	Cl	Cl	102 ± 40	190 ± 20	>2000
4s	CH_3	CH_3O	CH_3O	83 ± 20	>2000	>2000

Table 2. Comparison of Dopamine, Serotonin, and Norepinephrine Transporter Binding and Uptake Studies in C6hDAT, HEK-hSERT, and HEK-hNET Cells for WIN 35,065-2 Analogs[a]



				binding,[b] K_i (nM)			uptake,[b] IC_{50} (nM)		
cmpd	Z	X	Y	DAT	SERT	NET	[^{3}H]DA	[^{3}H]5HT	[^{3}H]NE
cocaine[c]				272 ± 60	601 ± 130	830 ± 147	267 ± 47	318 ± 57	385 ± 40
4a	Cl	H	H	18 ± 4	2670 ± 520	1840 ± 150	158 ± 63	2710 ± 500	750 ± 270
4b	Cl	F	H	12 ± 2	653 ± 80	1700 ± 90	30 ± 6	1010 ± 200	690 ± 190
4c	Cl	Cl	H	28 ± 3	2390 ± 580	2700 ± 400	41 ± 10	4400 ± 900	912 ± 40
4d	Cl	Br	H	35 ± 13	5700 ± 1800	3290 ± 390	107 ± 22	8220 ± 830	960 ± 300
4e	Cl	H	Br	39 ± 13	1500 ± 500	2530 ± 240	63 ± 28	4000 ± 1000	2300 ± 200
4f	Cl	NO_2	H	6.1 ± 2.3	1820 ± 140	2270 ± 380	30 ± 5	3600 ± 600	582 ± 94
4g	Cl	H	NO_2	7.7 ± 2.1	740 ± 110	2510 ± 370	45 ± 11	1610 ± 470	650 ± 160
4h	Cl	OCH_3	H	8.6 ± 2.7	5200 ± 1900	1270 ± 170	38 ± 18	6700 ± 700	620 ± 130
4i	Cl	Cl	Cl	66 ± 8	2710 ± 340	2300 ± 70	416 ± 82	5300 ± 1700	6500 ± 1000
4j	Cl	OCH_3	OCH_3	234 ± 74	3590 ± 490	1910 ± 200	212 ± 85	>6800	4210 ± 170
4k	CH_3	F	H	61 ± 18	1720 ± 600	1630 ± 380	181 ± 28	3200 ± 1300	4870 ± 840
4l	CH_3	Cl	H	212 ± 10	1320 ± 300	2870 ± 190	400 ± 100	377 ± 90	1170 ± 60
4m	CH_3	Br	H	130 ± 10	1870 ± 620	4240 ± 970	810 ± 290	1840 ± 500	1820 ± 410
4n	CH_3	H	Br	12 ± 3	870 ± 320	2210 ± 300	98 ± 11	3860 ± 500	3240 ± 280
4o	CH_3	NO_2	H	140 ± 40	1640 ± 160	1970 ± 660	197 ± 54	3170 ± 800	1550 ± 210
4p	CH_3	H	NO_2	14 ± 5	580 ± 160	990 ± 140	23 ± 5	2380 ± 190	2040 ± 240
4q	CH_3	OCH_3	H	53 ± 20	3670 ± 540	3630 ± 810	226 ± 77	6800 ± 1800	1810 ± 380
4r	CH_3	Cl	Cl	105 ± 47	2940 ± 340	>6100	469 ± 77	4400 ± 1100	4000 ± 2000
4s	CH_3	OCH_3	OCH_3	529 ± 31	7710 ± 410	1390 ± 300	885 ± 57	>10 000	>6900

[a] This data was supplied by the NIDA-CTDP program. Details of experimentals for these binding and uptake studies are given in ref 27. [b] Values for the mean ± standard error of three independent experiments, each conducted with triplicate determination. [c] Data taken from ref 27.

[^{3}H]paroxetine for the SERT, and 0.5 nM [^{3}H]nisoxetine for the NET. Results from this assay are listed in Table 1. In the second assay, the competition binding assays were determined using (h)DAT, (h)SERT, and (h)NET, stably expressed in HEK293 cells, and the nonselective radioligand [^{125}I]RTI-55 for the analogues **4b**−**s** (Table 2).[27] The HEK-(h)DAT, -(h)-SERT, and -(h)NET cells were also used to evaluate the compound's ability to block the reuptake of [^{3}H]dopamine ([^{3}H]-

DA), [^{3}H]serotonin ([^{3}H]5HT), and [^{3}H]norepinephrine ([^{3}H]-NE; Table 2).[27]

Results and Discussion

In our original studies of 3β-phenyl-2β-heterocyclic tropane analogs, we reported that the 2β-phenylthiazole **4a** could be easily synthesized using standard methods for preparing thiazoles. Specifically, the 3β-(4-chlorophenyl)tropane-2β-(*N*-phenacyl)-carboxamide was easily prepared and cyclized to the desired **4a** in good yield by using Lawesson's reagent. We anticipated that the aromatic substituted analogs **4b**−**s** could be prepared by a similar procedure and, indeed, we were able to obtain the 3β-(4-chlorophenyl) analogs **4b**−**d**, **4f**, and **4h** in satisfactory yield (Scheme 1). Surprisingly, when we tried this procedure on the 3β-(4-methylphenyl) analogs, the reactions became much more difficult to workup and the yields were unacceptable. Fortunately, we were able to develop a new synthesis of this class of compounds, which proceeded with much less difficulty and higher overall yields (Scheme 2). The key step in the new synthetic route was the conversion of the amides **7** to the thioamides **8**. This was achieved by first converting amide **7** to the triflate enolate, followed by treatment with hydrogen sulfide. Attempts to convert **7** to **8** using Lawesson's reagent, or phosphorus pentasulfide under a variety of conditions, including different solvents, were unsuccessful. Once the thioamides **8** were in hand, they were easily converted to the desired 2β-arylthiazole analogs by acid-catalyzed cyclization.

The 2β-arylthiazole analogs were evaluated for their monoamine transporter binding properties using rat brain tissue (Table 1) or cloned receptors (Table 2). All compounds tested, with the exception of the 3β-(4-chlorophenyl)-2β-(3,4-dichlorophenyl)thiazole analog **4i**, in the rat tissue assay had higher affinity for the DAT relative to the SERT and NET. With a few exceptions, the 2β-arylthiazole analogs tended to show lower IC_{50}s for the DAT in the rat brain tissues test than the K_is for the DAT in the cloned receptor assay. An analysis of the DAT affinities in Table 1 shows that 11 of the analogs evaluated in the rat brain DAT test had IC_{50}s of 20 nM or less. The rank order for these analogs is: **4p** > **4g** > **4a** > **4b** > **4n** > **4k** > **4h** > **4q** > **4e** > **4c** = **4f**. A similar analysis of the DAT affinities determined using cloned human transporters (Table 2) shows that seven of the same analogs had K_is of 20 nM or less, although their rank order was different: **4f** > **4g** > **4h** > **4n** = **4b** > **4p** > **4a**. These results show that the highest potency compounds were identified by either the rat brain tissue or the cloned receptor assays. The two most potent compounds in the rat brain tissue DAT test are the 3β-(4-methyl and 3β-4-chlorophenyl)-2β-(3-nitrophenyl)thiazole analogs **4p** and **4g**, which have IC_{50}s of 4 and 5 nM, respectively. In the case of the cloned transporter test, the 3β-(4-chlorophenyl)-2β-(4-nitrophenyl) and (4-methoxyphenyl)thiazole analogs **4f** and **4g** with K_i of 6.1 and 7.7 nM, respectively, possessed the highest affinity.

Similar to the radioligand binding data, all of the compounds **4a**−**s** were better uptake inhibitors at the (h)DAT relative to the (h)SERT and (h)NET (Table 2). Even though the rank order of potency in [^{3}H]DA uptake inhibition did not parallel the rank order in the DAT binding studies, the three most potent analogs, all of which showed IC_{50}s of less than 30 nM, are also the three analogs possessing the highest DAT affinity. The most potent analog in the [^{3}H]DA uptake inhibition study was the 3β-(4-methylphenyl)2β-(3-nitrophenyl)thiazole analog **4p**, with an IC_{50} of 23 nM. The rank order of the four most potent analogs is **4p** > **4b** = **4f** > **4h**. Thus, for determining activity at the DAT, binding or uptake yields comparable results.

The most DAT selective analog relative to SERT in the cloned receptor assay was the 3β-(4-chlorophenyl)-2β-(4-methoxyphenyl)thiazole analog **4h**, which showed a 600-fold preference for the DAT. The 3β-(4-chlorophenyl)-2β-(4-nitrophenyl)thiazole analog **4f** showed a 370-fold preference for the DAT relative to the NET and, thus, was the most DAT selective analog relative to the NET. In the monoamine uptake inhibition studies, the 3β-(4-chlorophenyl)-2β-(4-nitrophenyl)thiazole **4f** and the 3β-(4-methylphenyl)-2β-(3-nitrophenyl)thiazole **4p** both had greater than 100-fold selectivity for [^{3}H]DA uptake inhibition relative to [^{3}H]5HT inhibition. Analog **4p** also had 88-fold selectivity for [^{3}H]DA uptake inhibition relative to [^{3}H]NE uptake inhibition, whereas **4f** possessed only a 19-fold selectivity for [^{3}H]DA uptake inhibition. Analog **4p** was also highly selective in the rat brain tissue binding assay showing 2400- and 1000-fold selectivity for the DAT relative to the SERT and NET.

In summary, using the 3β-(4-chlorophenyl)-2β-phenylthiazole analog **4a** as a lead compound, a number of analogs were designed, synthesized, and evaluated for their monoamine transporter binding and monoamine uptake inhibition properties to gain a better understanding of the structure−activity relationship (SAR) for this class of compounds. While most of the 3β-(4-chlorophenyl)-2β-(substituted phenyl)thiazole analogs could be synthesized by standard methods used for the synthesis of thiazoles, a new method had to be developed to synthesize the 3β-(4-methylphenyl)-2β-(substituted phenyl)thiazole analogs. The key step in the synthesis was the conversion of an amide to the thioamide that could be cyclized to the desired target compounds. In general, the compounds showed higher DAT affinity relative to the SERT and NET and greater [^{3}H]DA uptake inhibition potency relative to [^{3}H]5HT and [^{3}H]NE uptake inhibition. Based on the functional monoamine uptake data, the most potent and DA selective ligand was the 3β-(4-methylphenyl)-2β-(3-nitrophenyl)thiazole analog **4p**. However, based on the monoamine transporter binding data, several other compounds were DAT selective relative to the SERT and NET. These compounds should not be overlooked as potential DAT selective compounds, because it is difficult to predict the pharmacokinetic and pharmacodynamic properties of compounds.

Experimental Section

Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were recorded on a 300 MHz (Bruker AVANCE 300) spectrometer. Chemical shift data for the proton resonances were reported in parts per million (δ) relative to internal $(CH_3)_4Si$ (δ 0.0). Optical rotations were measured on an AutoPol III polarimeter purchased from Rudolf Research. Elemental analyses were performed by Atlantic Microlab, Norcross, GA. Analytical thin-layer chromatography (TLC) was carried out on plates precoated with silica gel GHLF (250 μM thickness). TLC visualization was accomplished with a UV lamp or in an iodine chamber. All moisture-sensitive reactions were performed under a positive pressure of nitrogen maintained by a direct line from a nitrogen source. Anhydrous solvents and hydrogen sulfide gas were purchased from Aldrich Chemical Co.

3β-(4-Chlorophenyl)-2β-[5-(4-chlorophenyl)thiazol-2-yl]tropane (4c) Hydrochloride. To compound **5a** (3.0 g, 0.0107 mol) in CH_2Cl_2 (75 mL) was added oxalyl chloride (11.0 mL, 2 M in CH_2Cl_2, 0.0214 mol). The reaction mixture was stirred at rt for 2 h and concentrated in vacuo. The resulting acid chloride was redissolved in CH_2Cl_2 (50 mL), and 2-amino-4′-chloroacetophenone hydrochloride (4.93 g, 0.0239 mol) was added, followed by Et_3N (5.47 g, 0.0541 mol) in CH_2Cl_2 (50 mL). The reaction mixture was stirred at rt overnight, filtered, and concentrated in vacuo to afford

5.9 g of a red-orange amorphous solid, which was purified by column chromatography on silica gel, eluting with CH_2Cl_2−$CHCl_3$−MeOH−NH_4OH (50:40:9:1) to yield 3.7 g (80%) of **6c** as an orange amorphous solid.

Compound **6c** (3.7 g, 0.0086 mol) and Lawesson's reagent (13.9 g, 0.034 mol) were added to toluene (150 mL) and stirred at reflux for 6 h. The reaction mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel, eluting with hexane−Et_2O−Et_3N (10:9:1) to afford 1.28 g (35%) of **4c** as a white solid. The free base was dissolved in CH_2Cl_2 and treated with excess 2 M ethereal HCl. The mixture was concentrated and triturated with warm EtOAc, cooled, and filtered to yield 0.80 g of **4c**·HCl as a white solid: mp 142−143 °C; ^{1}H NMR ($CDCl_3$, free base) δ 7.57 (s, 1H), 7.51 (d, 2H), 7.34 (d, 2H), 7.08 (d, 2H), 6.80 (d, 2H), 3.50 (bd, 1H), 3.40 (bs, 1H), 3.20−3.53 (m, 2H), 2.55 (q, 1H), 2.10−2.42 (m, 2H), 2.35 (s, 3H), 1.57−1.90 (m, 3H); $[\alpha]_D$ = −25.3° (*c* 0.53, MeOH). Anal. ($C_{23}H_{23}Cl_3N_2S$·$2H_2O$) C, H, N, S.

3β-(4-Chlorophenyl)-2β-[5-(4-fluorophenyl)thiazol-2-yl]tropane (4b) Hydrochloride. Compound **4b** was prepared by a procedure analogous to that described for the preparation of **4c** to afford 23% of **4b** as a beige solid: mp (HCl salt) 188−190 °C; ^{1}H NMR ($CDCl_3$, free base) δ 7.53 (m, 3H), 7.08 (m, 4H), 6.80 (d, 2H), 3.50 (bd, 1H), 3.40 (bs, 1H), 3.23−3.40 (m, 2H), 2.65 (bs, 1H), 2.10−2.42 (m, 2H), 2.35 (s, 3H), 1.60−1.85 (m, 3H); $[\alpha]_D$ = −24.0° (*c* 0.47, MeOH). Anal. ($C_{23}H_{23}Cl_2FN_2S$·$0.5H_2O$) C, H, N.

3β-(4-Chlorophenyl)-2β-[5-(4-bromophenyl)thiazol-2-yl]tropane (4d) Hydrochloride. Compound **4d** was prepared by a procedure analogous to that described for **4c** to give 32% of **4d** as a white solid: mp (HCl salt) 114−116 °C; ^{1}H NMR ($CDCl_3$, free base) δ 7.60 (s, 1H), 7.46 (q, 4H), 7.08 (d, 2H), 6.80 (d, 2H), 3.50 (bd, 1H), 3.40 (bs, 1H), 3.24−3.42 (m, 2H), 2.30−2.42 (m, 2H), 2.35 (s, 3H), 1.65−1.85 (m, 3H); $[\alpha]_D$ −25.9° (*c* 0.78, MeOH). Anal. ($C_{23}H_{24}Cl_3BrN_2S$·H_2O) C, H, N, S.

3β-(4-Chlorophenyl)-2β-[5-(4-nitrophenyl)thiazol-2-yl]tropane (4f) Hydrochloride. Compound **4f** was prepared by a procedure analogous to that described for **4c** to give 23% of **4f** as a light yellow solid: mp (HCl salt) 180−183 °C; ^{1}H NMR ($CDCl_3$, free base) δ 8.24 (d, 2H), 7.71 (m, 3H), 7.10 (d, 2H), 6.82 (d, 2H), 3.55 (bd, 1H), 3.42 (bs, 1H), 3.27−3.41 (m, 2H), 2.22−2.40 (m, 2H), 2.37 (s, 3H), 1.63−1.87 (m, 3H); $[\alpha]_D$ −23.7° (*c* 0.38, MeOH). Anal. ($C_{23}H_{23}Cl_2N_3O_2S$·$1.75H_2O$) C, H, N, S.

3β-(4-Chlorophenyl)-2β-[5-(4-methoxyphenyl)thiazol-2-yl]tropane (4h) Hydrochloride. Compound **4h** was prepared by a procedure analogous to that described for **4c** to give 35% of **4h** as a beige solid: ^{1}H NMR ($CDCl_3$ free base) δ 7.50 (d, 2H J = 8.7 Hz), 7.49 (s, 1H), 7.08 (d, 2H, J = 8.5 Hz), 6.91 (d, 2H, J = 8.7 Hz), 6.82 (d, 2H, J = 8.5 Hz), 3.83 (s, 3H), 3.49 (m, 1H), 3.38 (m, 1H), 3.32 (m, 1H), 3.24 (m, 1H), 2.34 (s, 3H), 2.17−2.44 (m, 2H), 1.82 (m, 2H), 1.63 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 168.1, 159.3, 140.4, 139.7, 135.2, 131.9, 129.1, 128.1, 127.9, 125.2, 114.3, 65.8, 61.6, 55.4, 52.9, 41.7, 36.9, 35.1, 26.0, 25.5; mp (HCl salt) 171−173 °C; $[\alpha]_D$ −16.4° (*c* 0.75, MeOH). Anal. ($C_{24}H_{27}Cl_2N_2OS$·2HCl) C, H, N, S.

3β-(4-Methylphenyl)-2β-[5-(4-bromophenyl)thiazol-2-yl]tropane (4m) Tartrate. Compound **4m** was prepared by a procedure analogous to that described for **4c** except the compound was characterized as the tartrate salt: mp 190−193 °C, $[\alpha]_D^{20}$ −21.1 (*c* 0.5, CH_3OH); ^{1}H NMR ($CDCl_3$ free base) δ 7.58 (s, 1H), 7.49 (d, 2H, J = 8.8 Hz), 7.44 (d, 2H, J = 8.8 Hz), 6.93 (d, 2H, J = 7.9 Hz), 6.76 (d, 2H, J = 8.0 Hz), 3.51 (m, 1H), 3.49 (m, 1H), 3.31 (m, 1H), 3.23 (m, 1H), 2.35 (s, 3H), 2.22 (s, 3H), 2.15−2.45 (m, 2H), 1.84 (m, 2H), 1.63 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 170.0, 138.6, 138.5, 136.5, 135.7, 131.9, 131.6, 128.8, 127.9, 127.5, 121.3, 65.8, 61.8, 53.1, 41.7, 37.0, 35.1, 26.0, 25.6, 21.0. Anal. ($C_{28}H_{32}BrN_20_6$·$2.5H_2O$) C, H, N.

4-Nitrophenacyl Azide (10c). Into a 100-mL round-bottom flask was added 950 mg (3.9 mmol) of 4-nitrophenacyl bromide, 271 mg (4.3 mmol) of sodium azide, and 15 mL of DMSO. The reaction mixture was allowed to stir at room temperature for at least 30 min, 50 mL of ice water was added, and the aqueous layer was extracted with 125 mL of diethyl ether. The combined organic layers were washed with water and brine and dried with Na_2CO_3. The organic fractions were concentrated to a residue that was purified by flash chromatography using CH_2Cl_2 as the eluent to give 700 mg (87%) of **10c** as a slightly yellow powder: ^{1}H NMR ($CDCl_3$) δ 8.35 (d, 2H, J = 9 Hz), 8.10 (d, 2H, J = 9 Hz), 4.61 (s, 2H).

4-Fluorophenacyl Azide (10a). Using a procedure similar to that described for **10c**, 1.7 g (0.0078 mol) of 4-fluorophenacyl bromide was treated with NaN_3 to give 1.24 g (88%) of **10a** as yellow crystals: ^{1}H NMR ($CDCl_3$) δ 7.95 (m, 2H), 7.18 (m, 2H), 4.53 (s, 2H).

4-Chlorophenacyl Azide (10b). Using a procedure similar to that described for **10c**, 25 g (0.11 mol) of 4′-chlorophenacyl bromide was treated with NaN_3 to give 10.5 g (50%) of **10b** as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.85 (d, 2H, J = 8.7 Hz), 7.49 (d, 2H, J = 8.7 Hz), 4.53 (s, 2H).

4-Methoxyphenacyl Azide (10d). Using a procedure similar to that described for **10c**, 5.26 g (0.023 mol) of 4-methoxyphenacyl bromide was treated with sodium azide to give 4.1 g (93%) of **10d** as a light yellow powder: ^{1}H NMR ($CDCl_3$) δ 7.89 (d, 2H, J = 7.2 Hz), 6.96 (d, 2H, J = 7.2 Hz), 4.54 (s, 2H), 3.89 (s, 3H).

3-Bromophenacyl Azide (10e). Using a procedure similar to that described for **10c**, 2.2 g (0.008 mol) of 3-bromophenacyl bromide was treated with sodium azide to give 1.3 g (62%) of **10e** as a white powder: ^{1}H NMR ($CDCl_3$) δ 8.05 (m, 1H), 7.84 (d, 1H, J = 7.5 Hz), 7.77 (d, 1H), 7.37 (dd, 1H), 4.54 (s, 2H).

3-Nitrophenacyl Azide (10f). Using a procedure similar to that described for **10c**, 3.16 g (0.013 mol) of 3-nitrophenacyl bromide was treated with NaN_3 to give 1.80 g (68%) of **10f** as a yellow powder: ^{1}H NMR ($CDCl_3$) δ 8.74 (d, 1H, J = 1.8 Hz), 8.49 (dd, 1H, J = 8.1 Hz), 8.27 (d, 1H, J = 8.1 Hz), 7.75 (dd, 1H J = 8.1 Hz), 4.63 (s, 1H).

3,4-Dichlorophenacyl Azide (10g). Using a procedure similar to that described for **10c**, 2.14 g (0.008 mol) of 3,4-dichlorophenacyl bromide was treated with NaN_3 to give 881 mg (48%) of **10g** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 8.00 (d, 1H, J = 1.8 Hz), 7.73 (dd, 1H, J = 8.4 Hz), 7.59 (d, 1H, J = 8.1 Hz), 4.52 (s, 2H).

3,4-Dimethoxyphenacyl Azide (10h). Using a procedure similar to that described for **10c**, 11.1 g (0.043 mol) of 3,4-dimethoxyphenacyl bromide was treated with NaN_3 to give 8.29 g (87%) of **10h** as a yellow powder: ^{1}H NMR ($CDCl_3$) δ 7.52 (d, 1H, J = 2.1 Hz), 7.47 (dd, 1H, J = 8.4 Hz), 6.89 (d, 1H, J = 8.4 Hz), 4.53 (s, 2H), 3.96 (s, 3H), 3.95 (s, 3H).

4-Nitrophenacyl Azide Ethylene Ketal (11c). A solution of 473 mg (2.29 mmol) of **10c**, 2.3 mL (41.3 mmol) of ethylene glycol, and 3 mL (23.4 mmol) of BF_3·Et_2O in 20 mL of CH_2Cl_2 was allowed to stir for 2 days under a N_2 atmosphere at room temperature. Saturated $NaHCO_3$ solution was added, and the mixture was extracted with $CHCl_3$. The extracts were washed with water and brine and then dried (Na_2SO_4). Organic layers were concentrated to dryness to leave a residue that was purified by silica gel chromatography, eluting with a 0−25% EtOAc/hexanes gradient. Concentration of collected fractions yielded 395 mg (69%) of **11c** as white feathery crystals: ^{1}H NMR ($CDCl_3$) δ 8.23 (d, 2H, J = 8.7 Hz), 7.70 (d, 2H, J = 8.7 Hz), 4.22 (m, 2H), 3.92 (m, 2H), 3.46 (s, 2H).

4-Fluorophenacyl Azide Ethylene Ketal (11a). Using a procedure similar to that described for **11c**, 1.22 g (0.007 mol) of **10a** was converted to 1.33 g (87%) of **11a** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.48 (m, 2H), 7.05 (m, 2H), 4.18 (m, 2H), 3.90 (m, 2H), 3.42 (s, 2H).

4-Chlorophenacyl Azide Ethylene Ketal (11b). Using a procedure similar to that described for **11c**, 10.5 g (0.054 mol) of **10b** was converted to 6.2 g (54%) of **11b** as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.44 (d, 2H, J = 8.4 Hz), 7.34 (d, 2H, J = 8.4 Hz), 4.17 (m, 2H), 3.89 (m, 2H), 3.41 (s, 2H).

4-Methoxyphenacyl Azide Ethylene Ketal (11d). Using a procedure similar to that described for **11c**, 1.53 g (0.008 mol) of **10d** was converted to 1.32 g (70%) of **11d** as a clear oil that solidified to a white solid upon standing: ^{1}H NMR ($CDCl_3$) δ 7.42

(d, 2H, $J = 7.2$ Hz), 6.88 (d, 2H, $J = 7.2$ Hz), 4.15 (m, 2H), 3.90 (m, 2H), 3.81 (s, 3H), 3.42 (s, 2H).

3-Bromophenacyl Azide Ethylene Ketal (11e). Using a procedure similar to that described for **11c**, 980 mg (4.1 mmol) of **10e** was converted to 923 mg (80%) of **11e** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.66 (m, 1H), 7.46 (m, 2H), 7.25 (m, 1H), 4.18 (m, 2H), 3.90 (m, 2H), 3.41 (s, 2H).

3-Nitrophenacyl Azide Ethylene Ketal (11f). Using a procedure similar to that described for **11c**, 1.65 g (0.008 mol) of **10f** was converted to 1.29 g (64%) of **11f** as a yellow oil that solidified upon standing: ^{1}H NMR ($CDCl_3$) δ 8.39 (d, 1H, $J = 1.8$ Hz), 8.22 (dd, 2H, $J = 8.1$ Hz), 7.83 (d, 1H, $J = 1.8$ Hz), 7.58 (dd, 1H, $J = 1.8$ Hz), 4.23 (m, 2H), 3.93 (m, 2H), 4.46 (s, 2H).

3,4-Dichlorophenacyl Azide Ethylene Ketal (11g). Using a procedure similar to that described for **11c**, 720 mg (3.13 mmol) of **10g** was converted to 606 mg (71%) of **11g** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.60 (d, 1H, $J = 2.1$ Hz), 7.45 (d, 1H, $J = 8.4$ Hz), 7.32 (d, 1H, $J = 9$ Hz), 4.18 (m, 2H), 3.90 (m, 2H), 3.41 (s, 2H).

3,4-Dimethoxyphenacyl Azide Ethylene Ketal (11h). Using a procedure similar to that described for **11c**, 7.97 g (0.036 mol) of **10h** was converted to 7.6 g (80%) of **11h** as a white powder: ^{1}H NMR ($CDCl_3$) δ 7.06 (dd, 1H, $J = 8.1$ Hz), 7.01 (d, 1H, $J = 1.8$ Hz), 6.89 (d, 1H, $J = 8.1$ Hz), 4.17 (m, 2H), 3.92 (m, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 3.43 (s, 2H).

4-Nitrophenacylamine Ethylene Ketal (12c). A solution of 1.20 g (0.0048 mol) of **11c** was stirred with 1.36 g (0.0053 mol) of PPh_3 in 75 mL of dry THF for 1 day. The reaction mixture was concentrated to 10 mL, ~150 μL of water (an excess) was added, and the reaction mixture was allowed to stir overnight. The reaction mixture was evaporated to dryness, and the resulting residue was purified by flash chromatography on silica gel using 0−25% CMA gradient solution in CH_2Cl_2 (where CMA refers to 80:18:2 ratio of $CHCl_3$/MeOH/NH_4OH elution solvent). Isolated fractions provided 804 mg (75%) of **12c** as a pure, slightly yellow powder: ^{1}H NMR ($CDCl_3$) δ 8.21 (d, 1H, $J = 7.2$ Hz), 7.65 (d, 1H, $J = 7.2$ Hz), 4.11 (m, 2H), 3.84 (m, 2H), 2.92 (s, 2H), 1.39 (bs, 2H).

4-Fluorophenacylamine Ethylene Ketal (12a). Using a procedure similar to that described for **12c**, 1.32 g (0.006 mol) of **11a** was reduced to give 847 mg (73%) of **12a** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.42 (m, 2H), 7.3 (m, 2H), 4.05 (m, 2H), 3.84 (m, 2H), 2.89 (s, 2H), 1.40 (bs, 2H).

4-Chlorophenacylamine Ethylene Ketal (12b). Using a procedure similar to that described for **12c**, 10.5 g (0.054 mol) of **11b** was reduced to give 6.06 g (54%) of **12b** as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.44 (d, 2H, $J = 8.4$ Hz), 7.34 (d, 2H, $J = 8.4$ Hz), 4.17 (m, 2H), 3.89 (m, 2H), 3.41 (s, 2H), 1.34 (bs, 2H).

4-Methoxyphenacylamine Ethylene Ketal (12d). Using a procedure similar to that described for **12c**, 1.13 g (0.0048 mol) of **11d** was reduced to give 617 mg (61%) of **12d** as a white waxy solid: ^{1}H NMR ($CDCl_3$) δ 7.37 (d, 2H, $J = 8.7$ Hz), 6.88 (d, 2H, $J = 8.7$ Hz), 4.05 (m, 2H), 3.85 (m, 2H), 3.80 (s, 3H), 2.90 (s, 2H), 1.38 (bs, 2H).

3-Bromophenacylamine Ethylene Ketal (12e). Using a procedure similar to that described for **12c**, 923 mg (3.25 mmol) of **11e** was reduced to give 793 mg (95%) of **12e** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.61 (m, 2H), 7.43 (d, 1H), 7.38 (d, 1H), 7.21 (dd, 1H), 4.07 (m, 2H), 3.84 (m, 2H), 2.89 (s, 2H), 1.37 (bs, 2H).

3-Nitrophenacylamine Ethylene Ketal (12f). Using a procedure similar to that described for **12c**, 1.10 g (0.0042 mol) of **11f** was reduced to give 593 mg (60%) of **12f** as a white solid: ^{1}H NMR ($CDCl_3$) δ 8.34 (dd, 1H, $J = 1.8$ Hz), 8.19 (dd, 1H, $J = 8.1$ Hz), 7.80 (d, 1H, $J = 8.1$ Hz), 7.55 (dd, 1H, $J = 8.1$ Hz), 4.13 (m, 2H), 3.86 (m, 2H), 2.94 (s, 2H), 1.40 (bs, 2H).

3,4-Dichlorophenacylamine Ethylene Ketal (12g). Using a procedure similar to that described for **12c**, 606 mg (2.21 mmol) of **11g** was reduced to give 522 mg (95%) of **12g** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.55 (d, 1H, $J = 1.8$ Hz), 7.42 (d, 1H, $J = 8.1$ Hz), 7.27 (d, 1H, $J = 8.4$ Hz), 4.07 (m, 2H), 3.84 (m, 2H), 2.81 (s, 2H), 1.35 (bs, 2H).

3,4-Dimethoxyphenacylamine Ethylene Ketal (12h). Using a procedure similar to that described for **12c**, 6.63 g (0.025 mol) of **11h** was reduced to give 5.1 g (85%) of **12h** as a white powder: ^{1}H NMR ($CDCl_3$) δ 7.01 (dd, 1H, $J = 8.1$ Hz), 6.97 (d, 1H), 6.85 (d, 1H), 4.07 (m, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 3.86 (m, 2H), 2.92 (s, 2H), 1.34 (bs, 2H).

3β-(4-Methylphenyl)tropane-2β-*N*-4′-fluorophenacylcarboxamide Ethylene Ketal (7k). To a cooled solution (0 °C) of 260 mg (1 mmol) of **5b** and 198 mg (1 mmol) of **12a** in dry DMF was added 6 mL of a 3 M (1.8 mmol) HOAt followed by 650 mg (3.4 mmol) of EDCI. After stirring 2 days under N_2 at 25 °C, the reaction mixture was diluted with EtOAc and washed with saturated $NaHCO_3$ solution, water, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting residue was purified by flash chromatography on silica gel using 25−50% CMA solvent in CH_2Cl_2 as the eluent. Isolated fractions produced 341 mg (78%) of **7k** as a pure white solid: ^{1}H NMR ($CDCl_3$) δ 9.86 (bt, 1H), 7.53 (dd, 2H), 7.07−6.96 (m, 6H), 4.11 (m, 2H), 3.91 (m, 2H), 3.59 (m, 2H), 3.23 (t, 2H), 3.05 (m, 1H), 2.45 (dd, 1H), 2.26 (s, 3H), 2.20 (s, 3H), 2.14 (m, 3H), 1.72−1.56 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 129.3, 128.3, 128.0, 115.4, 65.5, 65.3, 64.3, 61.8, 54.9, 46.7, 41.5, 36.1, 35.6, 26.5, 25.4, 21.5; LCMS (ESI) *m*/*z* 439.7 $(M + 1)^+$.

3β-(4-Methylphenyl)tropane-2β-*N*-4′-fluorophenacylcarboxthioamide (8k). To a chilled (dry ice/acetonitrile) solution of 294 mg (0.67 mmol) of **7k** in 7 mL of CH_2Cl_2 containing 190 μL (2.38 mmol) of pyridine under N_2 was added 140 μL (0.84 mmol) of Tf_2O. The reaction mixture was slowly warmed to 0 °C and allowed to stir for 4 h in an ice bath. Hydrogen sulfide gas was bubbled through the solution. The reaction mixture was diluted with EtOAc, washed with $NaHCO_3$ solution, water, and brine, and dried (Na_2SO_4). The organic fractions were concentrated to dryness, and the residue was subjected to column chromatography on silica gel using 25−50% CMA solution in CH_2Cl_2 gradient. Recrystallization of dried product fractions from EtOAc/heptanes afforded 200 mg (66%) of **8k** as a tan solid: ^{1}H NMR ($CDCl_3$) δ 12.21 (bs, 1H), 7.56 (dd, 2H), 7.08 (dd, 2H, $J = 8.1$ Hz), 7.03 (d, 2H, $J = 8.1$ Hz), 6.92 (d, 2H, $J = 8.1$ Hz), 4.17 (m, 2H), 3.95 (m, 2H), 3.95 (d, 1H), 3.77 (d, 1H), 3.44 (d, 1H), 3.28 (m, 1H), 3.20 (d, 1H), 3.10 (m, 1H), 2.27 (s, 3H), 2.23 (s, 3H), 2.19 (m, 3H), 1.75 (m, 2H), 1.61 (dt, 1H); LCMS (ESI) *m*/*z* 455.4 $(M + 1)^+$.

3β-(4-Methylphenyl)-2β-[5-(4′-fluorophenyl)thiazol-2-yl]tropane (4k) Hydrochloride. A solution of 155 mg (0.354 mmol) of **8k** dissolved in 3 mL of 12 N HCl was heated to 65 °C for 0.5 h in a hot water bath. Ice was added directly to the solution, and the mixture was basified with 12 mL of 3 N NaOH. The basified solution was extracted with 3 × 25 mL EtOAc, and the combined organic layers were washed with saturated $NaHCO_3$, water, and brine and dried (Na_2SO_4). Solvent was evaporated to yield 122 mg (88%) of yellowish solid. To a solution of 53 mg (0.135 mol) of the solid in 2 mL of dry $CHCl_3$ was added an excess amount (3 to 6 equiv) of 1 M HCl in ether. The acidified solution was concentrated to remove any excess solvent and HCl. The final residue was washed once with dry diethyl ether and dried to give 48 mg (81%) of the hydrochloride salt of **4k** as a light tan solid: ^{1}H NMR ($CDCl_3$ free base) δ 7.52 (m, 3H), 7.06 (dd, 2H, $J = 6.9$ Hz), 6.92 (d, 1H, $J = 8.1$ Hz), 6.77 (d, 2H, $J = 8.1$ Hz), 3.50 (d, 1H), 3.38 (m, 1H), 3.29 (t, 1H), 3.25 (t, 1H), 2.38 (m, 1H), 2.34 (s, 3H), 2.24 (m, 2H), 2.21 (s, 3H), 1.83 (q, 2H), 1.62 (dt, 1H); ^{13}C NMR ($CDCl_3$) δ 136.40, 129.18, 128.57, 127.97, 116.32, 66.25, 62.16, 53.56, 42.16, 37.42, 35.58, 26.41, 25.98, 21.40; LCMS (ESI) *m*/*z* 393.7 $(M + 1)^+$. The hydrochloride salt had a mp of 220−222 °C; $[\alpha]^{20}_D$ −18.5° (*c* 0.20, CH_3OH). Anal. ($C_{24}H_{27}ClFN_2S\cdot 0.5H_2O$) C, H, N, S.

3β-(4-Methylphenyl)tropane-2β-*N*-4′-chlorophenacylcarboxamide Ethylene Ketal (7l). Using a procedure similar to that described for **7k**, 2.82 g (0.011 mol) of **5b** was coupled with 2.34 g (0.011 mol) of **12b** to give 3.24 g (65%) of **7l** as a white powder: ^{1}H NMR ($CDCl_3$) δ 9.87 (bt, 1H), 7.47 (d, 2H, $J = 8.4$ Hz), 7.34 (d, 2H, $J = 8.4$ Hz), 7.02 (d, 2H, $J = 8.1$ Hz), 6.96 (d, 2H, $J = 8.1$ Hz), 4.10 (m, 2H), 3.90 (m, 2H), 3.58 (d, 2H, $J = 5.1$ Hz), 3.24 (m, 2H), 3.03 (m, 1H), 2.45 (d, 1H), 2.26 (s, 3H), 2.19 (s, 3H), 2.14 (m, 3H), 1.75−1.55 (m, 3H); ^{13}C NMR ($CDCl_3$) δ

129.34, 128.76, 128.01, 65.51, 65.32, 64.32, 61.85, 54.84, 46.58, 41.49, 36.03, 35.60, 26.51, 25.37, 21.50; LCMS (ESI) *m*/*z* 456.1 $(M + 1)^+$.

3β-(4-Methylphenyl)tropane-2β-*N*-4-chlorophenacylcarboxthioamide Ethylene Ketal (8l). Using a procedure similar to that described for **8k**, 3.23 g (0.007 mol) of **7l** was converted to 1.58 g (47%) of **8l** as a beige solid: ^{1}H NMR ($CDCl_3$) δ 12.23 (bs, 1H), 7.53 (d, 2H, *J* = 8.4 Hz), 7.38 (d, 2H, *J* = 8.4 Hz), 7.02 (d, 2H, *J* = 8.5 Hz), 6.91 (d, 2H, *J* = 8.5 Hz), 4.17 (m, 2H), 3.97 (m, 3H), 3.75 (d, 1H), 3.43 (m, 1H), 3.29 (m, 1H), 3.21 (m, 1H), 3.10 (m, 1H), 2.27 (s, 3H), 2.22 (s, 3H), 2.10 (m, 3H), 1.73 (m, 2H), 1.58 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 129.23, 128.98, 128.29, 127.99, 65.55, 65.44, 62.06, 61.41, 53.75, 41.27, 36.59, 35.61, 26.57, 25.42, 21.52; LCMS (ESI) *m*/*z* 472.1 $(M + 1)^+$.

3β-(4-Methylphenyl)-2β-[5-(4-chlorophenyl)thiazol-2-yl]tropane (4l) Hydrochloride. Compound **8l** was cyclized using a procedure similar to that described for **4k** to give 750 mg of **4l** free base, which was converted to 739 mg (89%) of the hydrochloride salt as an off-white powder: ^{1}H NMR ($CDCl_3$ free base) δ 7.57 (s, 1H), 7.49 (d, 2H, *J* = 8.4 Hz), 7.34 (d, 2H, *J* = 8.4 Hz), 6.92 (d, 2H, *J* = 8.4 Hz), 6.76 (d, 2H, *J* = 8.4 Hz), 3.51 (m, 1H), 3.39 (m, 1H), 3.29 (m, 1H), 3.24 (t, 1H), 2.38 (m, 1H), 2.34 (s, 3H), 2.22 (s, 3H), 2.19 (m, 2H), 1.84 (m, 2H), 1.65 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 136.82, 129.40, 129.19, 128.04, 127.95, 66.22, 62.14, 53.58, 42.15, 37.39, 35.53, 26.39, 25.97, 21.40; LCMS (ESI) *m*/*z* 446.5 $(M + 1)^+$. The hydrochloride salt had a mp of 192−195 °C; $[\alpha]^{20}_D$ −22.5° (c 0.20, CH_3OH). Anal. ($C_{24}H_{26}Cl_2N_2S \cdot 0.5H_2O$) C, H, N, S.

3β-(4-Methylphenyl)tropane-2β-*N*-3′-bromophenylacylcarboxamide Ethylene Ketal (7n). Using a procedure similar to that described for **7k**, **5b** (1 mmol) was coupled to 260 mg (1 mmol) of **12e** to give 255 mg (52%) of **7n** as a white solid: ^{1}H NMR ($CDCl_3$) δ 9.88 (bt, 1H), 7.73 (dd, 1H, *J* = 1.8 Hz), 7.49−7.46 (m, 2H, *J* = 8.1 Hz), 7.28 (d, 1H, *J* = 8.1 Hz), 6.99 (d, 2H, *J* = 8.1 Hz), 6.91 (d, 2H, *J* = 8.1 Hz), 4.12 (m, 2H), 3.92 (m, 2H), 3.58 (m, 2H), 3.27 (m, 2H), 3.00 (m, 1H), 2.44 (dd, 1H), 2.26 (s, 3H), 2.21 (s, 3H), 2.13 (m, 3H), 1.74−1.55 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 131.91, 130.35, 129.77, 129.32, 128.00, 125.26, 65.53, 65.40, 64.29, 61.82, 54.84, 46.96, 41.44, 35.95, 35.61, 26.49, 25.39, 21.49; LCMS (ESI) *m*/*z* 499.6 $(M + 1)^+$.

3β-(4-Methylphenyl)tropane-2β-*N*-3′-bromophenylacylcarboxthioamine Ethylene Ketal (8n). Using a procedure similar to that described for **8k**, 268 mg (0.54 mmol) of **7n** was converted to 107 mg (68%) of **8n** as a tan solid: ^{1}H NMR ($CDCl_3$) δ 12.23 (bs, 1H), 7.78 (d, 1H, *J* = 1.8 Hz), 7.51 (m, 2H), 7.30 (dd, 1H, *J* = 7.8 Hz), 7.00 (d, 2H, *J* = 8.1 Hz), 6.82 (d, 2H, *J* = 8.1 Hz), 4.16 (m, 2H), 3.97 (m, 3H), 3.72 (dd, 1H), 3.42 (m, 1H), 3.32 (m, 1H), 3.16 (dd, 1H), 3.00 (m, 1H), 2.27 (s, 3H), 2.23 (s, 3H), 2.12 (m, 3H), 1.75 (m, 2H), 1.57 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 131.89, 130.17, 129.29, 128.83, 127.86, 124.86, 65.19, 65.13, 61.62, 61.07, 53.83, 40.87, 36.16, 35.13, 26.16, 25.06, 21.11; LCMS (ESI) *m*/*z* 515.7 $(M + 1)^+$.

3β-(4-Methylphenyl)-2β-[5-(3′-bromophenyl)thiazol-2-yl]tropane (4n) Hydrochloride. Using a procedure similar to that described for **4k,** 107 mg (0.208 mmol) of **8n** was cyclized to give 64 mg (67%) of **4n** free base: ^{1}H NMR ($CDCl_3$) δ 7.72 (dd, 1H, *J* = 1.8 Hz), 7.58 (s, 1H), 7.50 (dd, 1H, *J* = 1.8, 7.8 Hz), 7.38 (dd, 1H, *J* = 7.8 Hz), 7.22 (dd, 2H, *J* = 8.1 Hz), 6.92 (d, 2H, *J* = 8.1 Hz), 6.72 (d, 2H, *J* = 8.1 Hz), 3.51 (m, 1H), 3.38 (m, 1H), 3.25 (m, 2H), 2.43 (m, 1H), 2.35 (s, 3H), 2.22 (s, 3H), 2.17 (m, 2H), 1.83 (m 2H), 1.59 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 137.20, 130.72, 130.69, 129.67, 129.21, 127.93, 125.38, 66.19, 62.14, 53.62, 42.17, 37.41, 35.50, 26.39, 25.99, 21.40; LCMS (ESI) *m*/*z* 453.0 $(M + 1)^+$. The hydrochloride salt had a mp of 223−224 °C; $[\alpha]^{20}_D$ −20.0° (*c* 0.20, CH_3OH). Anal. ($C_{24}H_{26}BrClN_2S$) C, H, N, S.

3β-(4-Methylphenyl)tropane-2β-*N*-4-nitrophenacylcarboxamide Ethylene Ketal (7o). Using a procedure similar to that described for **7k**, 260 mg (1 mmol) of **5b** was coupled to 225 mg (1 mmol) of **12c** to give 415 mg (89%) of **7o** as a white solid: ^{1}H NMR ($CDCl_3$) δ 9.92 (bt, 1H), 8.21 (d, 2H, *J* = 9.3 Hz), 7.72 (d, 2H, *J* = 9.3 Hz), 7.01 (d, 2H, *J* = 8.4 Hz), 6.95 (d, 2H, *J* = 8.4 Hz), 4.15 (m, 2H), 3.89 (m, 2H), 3.60 (dd, 2H), 3.25 (m, 2H), 3.00 (m, 1H), 2.47 (d, 1H), 2.26 (s, 3H), 2.24 (s, 3H), 2.15 (m, 3H), 1.72−1.66 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 129.33, 127.88, 127.68, 123.79, 65.75, 65.56, 64.34, 61.85, 54.73, 46.31, 41.57, 35.96, 35.42, 26.49, 25.36, 21.47; LCMS (ESI) *m*/*z* 466.7 $(M + 1)^+$.

3β-(4-Methylphenyl)tropane-2β-*N*-4-nitrophenacylthiocarboxthioamide Ethylene Ketal (8o). Using a procedure similar to that described for **8k**, 328 mg (0.70 mmol) of **7o** was converted to 163 mg (48%) of **8o** as a tan solid: ^{1}H NMR ($CDCl_3$) δ 12.30 (bs, 1H), 8.26 (d, 2H, *J* = 9.3 Hz), 7.77 (d, 2H, *J* = 9.3 Hz), 7.02 (d, 2H, *J* = 8.4 Hz), 6.91 (d, 2H, *J* = 8.4 Hz), 4.23 (m, 2H), 3.98 (m, 3H), 3.86 (m, 1H), 3.45 (m, 1H), 3.33 (m, 1H), 3.24 (m, 1H), 3.15 (m, 1H), 2.27 (s, 3H), 2.25 (s, 3H), 2.21 (m, 3H), 1.70−1.56 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 129.24, 128.19, 127.70, 124.04, 65.67, 65.57, 62.06, 61.43, 53.36, 41.37, 35.53, 35.66, 26.59, 25.42, 21.51; LCMS (ESI) *m*/*z* 482.6 $(M + 1)^+$.

3β-(4-Methylphenyl)-2β-[5-(4′-nitrophenyl)thiazol-2-yl]tropane (4o) Hydrochloride. Using a procedure similar to that described for **4k**, 144 mg (0.30 mmol) of **8o** was cyclized to give 122 mg (97%) of **4o** free base, which was converted to the hydrochloride salt: ^{1}H NMR ($CDCl_3$ free base) δ 8.15 (d, 2H, *J* = 9.3 Hz), 7.65 (d, 2H, *J* = 9.3 Hz), 7.62 (s, 1H), 6.85 (d, 2H, *J* = 8.4 Hz), 6.69 (d, 2H, *J* = 8.4 Hz), 3.48 (m, 1H), 3.34 (m, 1H), 3.22 (m, 2H), 2.35 (m, 1H), 2.29 (s, 3H), 2.11 (s, 3H), 2.10 (m, 2H), 1.60 (m, 2H), 1.56 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 137.49, 127.80, 126.43, 125.58, 123.30, 64.67, 60.67, 52.23, 40.72, 35.91, 33.89, 24.92, 24.57, 19.97; LCMS (ESI) *m*/*z* 420.8 $(M + 1)^+$. The hydrochloride salt had a mp of 170−176 °C; $[\alpha]^{20}_D$ −16.5° (*c* 0.20, CH_3OH). Anal. ($C_{24}H_{26}ClN_3O_2S \cdot 2.5H_2O$) C, H, N, S.

3β-(4-Methylphenyl)tropane-2β-*N*-3-nitrophenacylcarboxamide Ethylene Ketal (7p). Using a procedure similar to that described for **8k**, 244 mg (1.09 mmol) of **5b** was coupled with **12f** to give 318 mg (63%) of **7p** as a white solid: ^{1}H NMR ($CDCl_3$) δ 9.99 (bt, 1H), 8.43 (s, 1H), 8.18 (d, 1H, *J* = 8.1 Hz), 7.87 (d, 1H, *J* = 8.1 Hz), 7.56 (dd, 1H, *J* = 8.1 Hz), 7.99 (d, 2H, *J* = 8.1 Hz), 6.90 (d, 2H, *J* = 8.1 Hz), 4.16 (m, 2H), 3.92 (m, 2H), 3.68 (dd, 1H), 3.58 (dd, 1H), 3.28 (m, 1H), 3.21 (m, 1H), 3.00 (m, 1H), 2.42 (dd, 1H), 2.26 (s, 3H), 2.25 (s, 3H), 2.12 (m, 3H), 1.72 (m, 2H), 1.61 (dt, 1H); ^{13}C NMR ($CDCl_3$) δ 132.90, 129.80, 129.32, 127.87, 123.90, 121.71, 65.74, 65.61, 64.25, 61.82, 54.70, 46.63, 41.48, 35.89, 35.43, 26.48, 25.36, 21.47; LCMS (ESI) *m*/*z* 466.7 $(M + 1)^+$.

3β-(4-Methylphenyl)tropane-2β-*N*-(3-nitrophenacyl)carboxthioamide Ethylene Ketal (8p). Using a procedure similar to that described for **8k**, 303 mg (0.70 mmol) of **7p** was converted to 141 mg (45%) of **8p** as a tan solid: ^{1}H NMR ($CDCl_3$) δ 9.99 (bt, 1H), 8.49 (dd, 1H, *J* = 1.8 Hz), 8.25 (dd, 1H, *J* = 1.8, 8.4 Hz), 7.94 (dd, 1H, *J* = 1.8, 8.4 Hz), 7.62 (dd, 1H, *J* = 8.4 Hz), 7.99 (d, 2H, *J* = 8.4 Hz), 6.83 (d, 2H, *J* = 8.4 Hz), 4.23 (m, 2H), 3.99 (m, 2H), 3.85 (d, 1H), 3.80 (d, 1H), 3.45 (d, 1H), 3.31 (m, 1H), 3.19 (m, 1H), 3.07 (m, 1H), 2.28 (s, 3H), 2.26 (s, 3H), 2.14 (m, 3H), 1.76 (m, 2H), 1.61 (dt, 1H); ^{13}C NMR ($CDCl_3$) δ 132.81, 130.09, 129.22, 128.15, 124.24, 121.65, 65.76, 65.11, 65.61, 62.03, 61.38, 53.79, 41.26, 36.46, 35.54, 26.51, 25.41, 21.48; LCMS (ESI) *m*/*z* 482.6 $(M + 1)^+$.

3β-(4-Methylphenyl)-2β-[5-(3-nitrophenyl)thiazol-2-yl]tropane (4p) Hydrochloride. Using a procedure similar to that described for **4k**, 132 mg (0.274 mmol) of **8p** was cyclized to give 88 mg (76%) of **4p** free base, which yielded 65 mg (65%) of the hydrochloride salt as a white solid: ^{1}H NMR ($CDCl_3$ free base) δ 8.41 (s, 1H), 8.12 (dd, 1H, *J* = 1.8, 7.5 Hz), 7.88 (d, 1H, *J* = 7.5 Hz), 7.70 (s, 1H), 7.54 (dd, 1H, *J* = 7.5 Hz), 6.94 (d, 2H, *J* = 8.1 Hz), 6.77 (d, 2H, *J* = 8.1 Hz), 3.54 (m, 1H), 3.42 (m, 1H), 3.30 (m, 1H), 3.26 (m, 1H), 2.43 (s, 3H), 2.29 (m, 3H), 2.23 (s, 3H), 1.85 (m, 2H), 1.64 (dt, 1H); ^{13}C NMR ($CDCl_3$) δ 138.03, 132.42, 130.19, 129.24, 127.89, 122.33, 121.49, 66.15, 62.13, 53.64, 42.17, 37.35, 35.36, 26.37, 26.00, 21.40; LCMS (ESI) *m*/*z* 420.9 $(M + 1)^+$. The hydrochloride salt had a mp of 208−211 °C; $[\alpha]^{20}_D$ −10.5° (*c* 0.20, CH_3OH). Anal. ($C_{24}H_{26}ClN_3O_2S \cdot 1H_2O$) C, H, N, S.

3β-(4-Methylphenyl)tropane-2β-*N*-4-methoxyphenacyl)carboxamide Ethylene Ketal (7q). Using a procedure similar to that

described for **7k**, 250 mg (1 mmol) of **5b** was coupled with 250 mg (1 mmol) of **12d** to give 286 mg (53%) of **7q** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 9.87 (bt, 1H), 7.47 (d, 2H, J = 8.1 Hz), 7.02 (d, 2H, J = 8.1 Hz), 6.98 (d, 2H, J = 8.1 Hz), 6.89 (d, 2H, J = 8.1 Hz), 4.11 (m, 2H), 3.92 (m, 2H), 3.81 (s, 3H), 3.59 (d, 2H, J = 5.1 Hz), 3.24 (m, 2H), 3.00 (m, 1H), 2.44 (dd, 1H), 2.28 (s, 3H), 2.19 (s, 3H), 2.15 (m, 3H), 1.70 (m, 2H), 1.60 (dt, 1H); ^{13}C NMR ($CDCl_3$) δ 129.33, 128.10, 127.76, 113.93, 65.37, 65.19, 64.31, 61.85, 55.71, 54.90, 46.77, 41.49, 36.08, 35.71, 26.53, 25.38, 21.50; LCMS (ESI) m/z 451.5 $(M + 1)^+$.

3β-(4-Methylphenyl)tropane-2β-*N*-(4-methoxyphenacyl)carboxthioamide Ethylene Ketal (8q). Using a procedure similar to that described for **8k**, 280 mg (0.62 mmol) of **7q** was converted to 83 mg (29%) of **8q** as a tan solid: ^{1}H NMR ($CDCl_3$) δ 12.14 (bs, 1H), 7.50 (d, 2H, J = 8.1 Hz), 7.02 (d, 2H, J = 8.1 Hz), 6.92 (d, 4H, J = 8.4 Hz), 4.14 (m, 2H), 3.96 (m, 3H), 3.81 (s, 3H), 3.75 (d, 1H), 3.44 (d, 1H), 3.28 (m, 1H), 3.20 (dd, 1H), 3.09 (m, 1H), 2.27 (s, 3H), 2.21 (s, 3H), 2.14 (m, 3H), 1.72 (m, 2H), 1.57 (dt, 1H); ^{13}C NMR ($CDCl_3$) δ 129.21, 128.35, 127.76, 114.11, 65.57, 65.32, 65.27, 62.09, 61.32, 55.77, 53.98, 41.23, 36.62, 35.56, 26.55, 25.41, 21.51; LCMS (ESI) m/z 467.6 $(M + 1)^+$.

3β-(4-Methylphenyl)-2β-[5-(4-methoxyphenyl)thiazol-2-yl]tropane (4q) Hydrochloride. Using a procedure similar to that described for **4k**, 110 mg (0.24 mmol) of **8q** was cyclized to give 72 mg (75%) of **4q** free base, which was converted to the hydrochloride salt: ^{1}H NMR ($CDCl_3$) δ 7.50 (d, 2H J = 8.7 Hz), 7.49 (s, 1H), 6.92 (d, 2H, J = 8.1 Hz), 6.89 (d, 2H, J = 8.1 Hz), 6.77 (d, 2H, J = 8.1 Hz), 3.83 (s, 3H), 3.49 (m, 1H), 3.38 (m, 1H), 3.30 (m, 1H), 3.22 (m, 1H), 2.41 (m, 1H), 2.33 (s, 3H), 2.25 (m, 2H), 2.21 (s, 3H), 1.83 (m, 2H), 1.60 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 135.55, 129.15, 128.13, 128.01, 114.72, 66.31, 62.18, 55.79, 53.55, 42.15, 37.46, 35.69, 26.42, 25.95, 21.39; LCMS (ESI) m/z 405.7 $(M + 1)^+$. The hydrochloride salt had a mp of 155−160 °C; $[\alpha]^{20}_D$ −14.5° (c 0.20, CH_3OH). Anal. ($C_{25}H_{30}ClN_2OS\cdot1.5H_2O$) C, H, N, S.

3β-(4-Methylphenyl)tropane-2β-*N*-(3,4-dichlorophenacyl)carboxamide Ethylene Ketal (7r). Using a procedure similar to that described for **7k**, 1.04 g (0.004 mol) of **5b** was coupled with 1.0 g (0.004 mol) of **12g** to give 1.33 g (67%) of **7r** as a white powder: ^{1}H NMR ($CDCl_3$) δ 9.86 (bt, 1H), 7.66 (d, 1H, J = 1.8 Hz), 7.45 (d, 1H, J = 8.1 Hz), 7.36 (d, 1H, J = 8.1 Hz), 7.01 (d, 2H, J = 8.4 Hz), 6.95 (d, 2H, J = 8.4 Hz), 4.10 (m, 2H), 3.91 (m, 2H), 3.57 (d, 2H, J = 5.4 Hz), 3.29 (m, 1H), 3.23 (m, 1H), 3.03 (m, 1H), 2.45 (dd, 1H, J = 6.9 Hz), 2.26 (s, 3H), 2.21 (s, 3H), 2.15 (m, 3H), 1.65 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 130.77, 129.34, 128.81, 127.94, 126.08, 65.62, 65.46, 64.30, 61.83, 54.78, 46.65, 41.47, 35.91, 35.51, 26.91, 25.37, 21.51; LCMS (ESI) m/z 489.3 $(M + 1)^+$.

3β-(4-Methylphenyl)tropane-2β-*N*-(3,4-dichlorophenacyl)carboxthioamide Ethylene Ketal (8r). Using a procedure similar to that described for **8k**, 977 mg (2.0 mmol) of **7r** was converted to 597 mg (59%) of **8r** as a beige crystalline powder: ^{1}H NMR ($CDCl_3$) δ 12.24 (bs, 1H), 7.71 (d, 1H, J = 1.8 Hz), 7.49 (d, 1H, J = 8.4 Hz), 7.41 (dd, 1H, J = 2.1 Hz, 8.4 Hz), 7.02 (d, 2H, J = 7.8 Hz), 6.87 (d, 2H, J = 7.8 Hz), 4.17 (m, 2H), 3.95 (m, 3H), 3.75 (dd, 1H, J = 15 Hz), 3.42 (m, 1H), 3.32 (m, 1H), 3.21 (m, 1H), 3.08 (m, 1H), 2.27 (s, 3H), 2.23 (s, 3H), 2.15 (m, 3H), 1.68 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 130.57, 128.82, 128.33, 127.80, 125.62, 65.19, 65.17, 65.13, 61.61, 61.03, 53.42, 40.86, 36.11, 35.13, 26.14, 26.02, 21.09; LCMS (ESI) m/z 505.6 $(M + 1)^+$.

3β-(4-Methylphenyl)-2β-[5-(3,4-dichlorophenyl)thiazol-2-yl]tropane (4r) Hydrochloride. Using a procedure similar to that described for **4k**, 567 mg (1.18 mmol) of **8r** was cyclized to give 505 mg of **4r** free base, which was converted to 410 mg (75%) of the hydrochloride salt: ^{1}H NMR ($CDCl_3$ free base) δ 7.65 (d, 1H, J = 1.5 Hz), 7.56 (s, 1H), 7.40 (m, 2H), 6.92 (d, 2H, J = 8.1 Hz), 6.75 (d, 2H, J = 8.1 Hz), 3.51 (m, 1H), 3.39 (m, 1H), 3.25 (m, 2H), 2.42 (m, 1H), 2.35 (s, 3H), 2.22 (s, 3H), 2.19 (m, 2H), 1.84 (m, 2H), 1.64 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 137.43, 131.11, 129.21, 128.43, 127.90, 125.95, 66.16, 62.13, 53.60, 42.16, 37.37, 35.43, 26.37, 25.99, 21.40; LCMS (ESI) m/z 443.8 $(M + 1)^+$. The hydrochloride salt had a mp of 214−216 °C; $[\alpha]^{20}_D$ −13.0° (c 0.20, CH_3OH). Anal. ($C_{24}H_{25}Cl_3N_2S$) C, H, N, S.

3β-(4-Methylphenyl)tropane-2β-*N*-3,4-dimethoxyphenacylcarboxamide Ethylene Ketal (7s). Using a procedure similar to that described for **7k**, 893 mg (3.44 mmol) of **5b** was coupled to 825 mg (3.44 mmol) of **12h** to give 1.42 g (86%) of **7s** as a clear viscous oil: ^{1}H NMR ($CDCl_3$) δ 9.86 (bt, 1H), 7.11 (dd, 1H, J = 2.1, 8.1 Hz), 7.05 (d, 1H, J = 2.1 Hz), 6.99 (d, 2H, J = 9 Hz), 6.98 (d, 2H, J = 9 Hz), 6.86 (d, 1H, J = 8.1 Hz), 4.10 (m, 2H), 3.94 (m, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 3.61 (d, 2H, J = 5.1 Hz), 3.25 (m, 2H), 3.03 (m, 1H), 2.46 (dd, 1H, J = 6.6 Hz), 2.26 (s, 3H), 2.15 (s, 3H), 2.10 (m, 3H), 1.70 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 129.32, 128.08, 118.85, 111.11, 109.69, 65.44, 65.22, 65.36, 61.87, 56.37, 54.91, 46.61, 41.51, 36.12, 35.68, 26.53, 25.37, 21.50; LCMS (ESI) m/z 481.5 $(M + 1)^+$.

3β-(4-Methylphenyl)tropane-2β-*N*-3,4-dimethoxyphenacylcarboxthioamide Ethylene Ketal (8s). Using a procedure similar to that described for **4k**, 1.05 g (0.0021 mol) of **7s** was converted to 520 mg (47%) of **8s** as a tan crystalline solid: ^{1}H NMR ($CDCl_3$) δ 12.21 (bs, 1H), 7.15 (dd, 1H, J = 2.1, 8.1 Hz), 7.08 (d, 1H, J = 2.1 Hz), 7.02 (d, 2H, J = 7.8 Hz), 6.95 (d, 2H, J = 7.8 Hz), 6.90 (d, 1H, J = 8.1 Hz), 4.16 (m, 2H), 3.99 (m, 2H), 3.98 (m, 1H), 3.93 (s, 3H), 3.89 (s, 3H), 3.81 (d, 1H), 3.43 (d, 1H), 3.27 (m, 1H), 3.20 (m, 1H), 3.09 (m, 1H), 2.27 (s, 3H), 2.21 (s, 3H), 2.10 (m, 3H), 1.70 (m, 2H), 1.60 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 129.92, 129.05, 119.62, 111.196, 110.37, 66.27, 66.09, 66.04, 62.80, 62.21, 57.16, 54.59, 42.02, 37.35, 36.35, 27.30, 26.14, 22.23; LCMS (ESI) m/z 497.8 $(M + 1)^+$.

3β-(4-Methylphenyl)-2β-[5-(3,4-dimethoxyphenyl)thiazol-2-yl]tropane (4s) Dihydrochloride. Using a procedure similar to that described for **4k**, 520 mg (1.03 mmol) of **8s** was cyclized to 450 mg of **4s** free base, which was converted to 450 mg (82%) of the dihydrochloride salt: ^{1}H NMR ($CDCl_3$ free base) δ 7.50 (s, 1H), 7.14 (dd, 1H, J = 2.1, 8.1 Hz), 7.05 (d, 1H, J = 2.1 Hz), 6.92 (d, 2H, J = 7.8 Hz), 6.86 (d, 1H, J = 8.4 Hz), 6.77 (d, 2H, J = 7.8 Hz), 3.95 (s, 3H), 3.90 (s, 3H), 3.50 (m, 1H), 3.39 (m, 1H), 3.31 (m, 1H), 3.23 (m, 1H), 2.42 (m, 1H), 2.34 (s, 3H), 2.22 (s, 3H), 2.16 (m, 2H), 1.82 (m, 2H), 1.63 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 135.72, 129.17, 128.02, 119.61, 111.99, 110.31, 66.31, 62.17, 56.51, 56.45, 53.56, 42.17, 37.45, 35.70, 26.43, 25.85, 21.40; LCMS (ESI) m/z 435.7 $(M + 1)^+$. The dihydrochloride salt had a mp of 140−148 °C; $[\alpha]^{20}_D$ −7.5° (c 0.20, CH_3OH). Anal. ($C_{25}H_{32}Cl_2N_2O_2S\cdot1.25H_2O$) C, H, N, S.

3β-(4-Chlorophenyl)tropane-2β-*N*-3-bromophenacylcarboxamide Ethylene Ketal (7e). Using a procedure similar to that described for **7k**, 279 mg (1 mmol) of **5a** was coupled with 259 mg (1 mmol) of **12e** to give 145 mg (28%) of **7e** as a white solid: ^{1}H NMR ($CDCl_3$) δ 9.89 (bt, 1H), 7.73 (dd, 1H, J = 1.8 Hz), 7.48 (dd, 2H, J = 1.8, 7.8 Hz), 7.28 (dd, 1H, J = 7.8 Hz), 7.14 (d, 2H, J = 8.4 Hz), 6.95 (d, 2H, J = 8.4 Hz), 4.11 (m, 2H), 3.91 (m, 2H) 3.65 (dd, 1H), 3.55 (dd, 1H), 3.30 (m, 1H), 3.24 (dd, 1H), 3.00 (m, 1H), 2.43 (dd, 1H), 2.20 (s, 3H), 2.11 (m, 3H), 1.70−1.59 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 131.96, 130.42, 129.76, 129.53, 128.69, 125.25, 65.53, 65.40, 64.19, 61.69, 54.62, 47.00, 41.39, 35.85, 35.50, 26.46, 25.35; LCMS (ESI) m/z 521.7 $(M + 1)^+$.

3β-(4-Chlorophenyl)tropane-2β-*N*-3-bromophenacylcarboxthioamide Ethylene Ketal (8e). Using a procedure similar to that described for **8k**, 140 mg (0.270 mmol) of **7e** was converted to 61 mg (42%) of **8e** as a tan solid: ^{1}H NMR ($CDCl_3$) δ 12.23 (bs, 1H), 7.77 (dd, 1H), 7.51 (dd, 2H, J = 1.5, 7.8 Hz), 7.31 (dd, 1H J = 7.8 Hz), 7.16 (d, 2H, J = 8.4 Hz), 6.86 (d, 2H, J = 8.4 Hz), 4.16 (m, 2H), 3.96 (m, 3H), 3.67 (d, 1H), 3.43 (d, 1H), 3.33 (m, 1H), 3.15 (d, 1H), 3.07 (m, 1H), 2.23 (s, 3H), 2.08 (m, 3H), 1.74−1.55 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 131.93, 130.22, 129.33, 129.26, 128.21, 124.84, 65.18, 65.13, 61.46, 60.81, 53.82, 40.80, 35.95, 35.92, 26.12, 25.00; LCMS (ESI) m/z 535.3 $(M + 1)^+$.

3β-(4-Chlorophenyl)-2β-[5-(3-bromo-2-thiazol)-2-yl]tropane (4e) Hydrochloride. Using a procedure similar to that described for **4k**, 61 mg (0.114 mmol) of **8e** was cyclized to give 36 mg (67%) of **4e** free base, which was converted to the hydrochloride salt as a tan solid: ^{1}H NMR ($CDCl_3$ free base) δ

7.72 (dd, 1H), 7.59 (s, 1H), 7.50 (dd, 1H, J = 1.5, 6.9 Hz), 7.41(d, 1H, J = 1.5, 6.9 Hz), 7.21 (dd, 1H, J = 7.8 Hz), 7.08 (d, 2H, J = 8.4 Hz), 6.80 (d, 2H, J = 8.4 Hz), 3.50 (dd, 1H), 3.40 (m, 1H), 3.31 (t, 1H), 3.24 (t, 1H), 2.35 (s, 3H), 2.23 (m, 3H), 1.82 (m, 2H), 1.64 (dt, 1H); ^{13}C NMR ($CDCl_3$) δ 137.24, 130.83, 130.76, 129.71, 129.41, 128.58, 125.36, 66.08, 62.00, 53.39, 42.13, 37.27, 35.32, 26.38, 25.93; LCMS (ESI) m/z 475.8 $(M + 1)^+$. The hydrochloride salt had a mp of 185−200 °C; $[\alpha]^{20}_D$ −26.5° (c 0.20, CH_3OH). Anal. ($C_{23}H_{23}BrCl_2N_2S\cdot 2.0H_2O$) C, H, N, S.

3β-(4-Chlorophenyl)tropane-2β-*N*-(3-nitrophenacyl)carboxamide Ethylene Ketal (7g). Using a procedure similar to that described for **7k**, 321 mg (1.15 mmol) of **5a** was coupled with 257 mg (1.15 mmol) of **12f** to give 128 mg (23%) of **7g** as a white solid: ^{1}H NMR ($CDCl_3$) δ 9.98 (bt, 1H), 8.42 (dd, 1H, J = 2.1 Hz), 8.20 (dd, 1H, J = 2.1, 7.5 Hz), 7.87 (dd, 1H, J = 2.1, 7.5 Hz), 7.56 (dd, 1H, J = 7.5 Hz), 7.14 (d, 1H, J = 8.7 Hz), 6.97 (d, 2H, J = 8.7 Hz), 4.16 (m, 2H), 3.92 (m, 2H) 3.64 (dd, 1H), 3.56 (dd, 1H), 3.29 (m, 1H), 3.23 (dd, 1H), 3.00 (m, 1H), 2.43 (dd, 1H), 2.25 (s, 3H), 2.14 (m, 3H), 1.67 (m, 3H); LCMS (ESI) m/z 486.5 $(M + 1)^+$.

3β-(4-Chlorophenyl)tropane-2β-*N*-(3-nitrophenacyl)carboxthioamide Ethylene Ketal (8g). Using a procedure similar to that described for **8k**, 256 mg (0.53 mmol) of **7g** was converted to 155 mg (54%) of **8g** as a tan solid: ^{1}H NMR ($CDCl_3$) δ 12.34 (bs, 1H), 8.48 (dd, 1H, J = 2.1 Hz), 8.25 (dd, 1H, J = 2.1, 7.5 Hz), 7.91 (dd, 1H, J = 2.1, 7.5 Hz), 7.62 (dd, 1H, J = 7.8 Hz), 7.15 (d, 2H, J = 8.1 Hz), 6.89 (d, 2H, J = 8.1 Hz), 4.22 (m, 2H), 3.97 (m, 3H), 3.82 (d, 1H), 3.44 (d, 1H), 3.31 (m, 1H), 3.18 (d, 1H), 3.10 (m, 1H), 2.27 (s, 3H), 2.10 (m, 3H), 1.75 (m, 2H), 1.54 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 132.82, 130.16, 129.63, 128.60, 124.28, 121.61, 65.74, 65.72, 65.46, 61.86, 61.17, 53.76, 41.25, 36.31, 35.42, 26.52, 25.37; LCMS (ESI) m/z 503.0 $(M + 1)^+$.

3β-(4-Chlorophenyl)-2β-[5-(3-nitrophenylthiazol)-2-yl]tropane (4g) Hydrochloride. Using a procedure similar to that described for **4k**, 155 mg (0.31 mmol) of **8g** was cyclized to give 104 mg (76%) of **4g** free base, which was converted to the hydrochloride salt as a tan solid: ^{1}H NMR ($CDCl_3$ free base) δ 8.41 (dd, 1H, J = 1.8 Hz), 8.13 (dd, 1H, J = 1.8 Hz), 7.89 (dd, 1H, J = 1.8, 8.4 Hz), 7.70 (s, 1H, J = 7.5 Hz), 7.57 (dd, 1H, J = 7.5 Hz), 7.10 (d, 2H, J = 6.9 Hz), 6.82 (d, 2H, J = 6.9 Hz), 3.54 (dd, 1H), 3.43 (m, 1H), 3.31 (m, 1H), 3.27 (t, 1H), 2.37 (s, 3H), 2.22 (m, 3H), 1.85 (m, 2H), 1.65 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 138.06, 132.36, 130.24, 129.37, 127.62, 122.45, 121.55, 66.03, 61.98, 53.42, 42.15, 37.19, 35.18, 26.36, 25.95; LCMS (ESI) m/z 440.6 $(M + 1)^+$. The hydrochloride salt had a mp of 160−162 °C; $[\alpha]^{20}_D$ −25.5° (c 0.20, CH_3OH). Anal. ($C_{23}H_{24}Cl_3N_3O_2S\cdot 1.5H_2O$) C, H, N, S.

3β-(4-Chlorophenyl)tropane-2β-*N*-(3,4-dichlorophenacyl)carboxamide Ethylene Ketal (7i). Using a procedure similar to that described for **7k**, 1.19 g (0.0043 mol) of **5a** was coupled with 1.04 g (0.0043 mol) of **12g** to give 0.83 g (39%) of **7i** as a white powder: ^{1}H NMR ($CDCl_3$) δ 9.88 (bt, 1H), 7.65 (d, 1H, J = 1.8 Hz), 7.46 (d, 1H, J = 8.1 Hz), 7.36 (dd, 1H, J = 2.1 Hz, 8.1 Hz), 7.17 (d, 2H, J = 8.4 Hz), 7.00 (d, 2H, J = 8.4 Hz), 4.12 (m, 2H), 3.90 (m, 2H), 3.58 (m, 2H), 3.29 (m, 1H), 3.24 (m, 1H), 3.03 (m, 1H), 2.45 (dd, 1H, J = 9 Hz), 2.21 (s, 3H), 2.13 (m, 3H), 1.65 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 130.45, 129.10, 128.42, 128.33, 125.68, 65.23, 65.07, 63.83, 61.32, 54.19, 46.28, 41.03, 35.46, 35.04, 26.08, 24.96; LCMS (ESI) m/z 511.3 $(M + 1)^+$.

3β-(4-Chlorophenyl)tropane-2β-*N*-(3,4-dichlorophenacyl)carboxthioamide Ethylene Ketal (8i). Using a procedure similar to that described for **8k**, 835 mg (1.64 mmol) of **7i** was converted to 366 mg (42%) of **8i** as a beige crystalline solid: ^{1}H NMR ($CDCl_3$) δ 12.22 (bs, 1H), 7.70 (d, 1H, J = 1.8 Hz), 7.50 (d, 1H, J = 8.1 Hz), 7.41 (dd, 1H, J = 1.8, 8.1 Hz), 7.16 (d, 2H, J = 8.4 Hz), 6.92 (d, 2H, J = 8.4 Hz), 4.17 (m, 2H), 3.9 (m, 3H), 3.72 (dd, 1H, J = 2.4, 15 Hz), 3.43 (bd, 1H), 3.41 (m, 1H), 3.20 (bd, 1H), 3.10 (m, 1H), 2.22 (s, 3H), 2.10(m, 3H), 1.7 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 131.03, 129.70, 128.71, 128.60, 126.01, 65.58, 65.43, 61.87, 61.21, 53.81, 41.21, 36.34, 35.37, 26.52, 25.38; LCMS (ESI) m/z 527.6 $(M + 1)^+$.

3β-(4-Chlorophenyl)-2β-[5-(3,4-dichlorophenyl)thiazol-2-yl]tropane (4i) Hydrochloride. Using a procedure similar to that described for **4k**, 619 mg (1.18 mmol) of **8i** was cyclized to give 501 mg (92%) of **4i** free base, which was converted to the hydrochloride salt as a white solid: ^{1}H NMR ($CDCl_3$ free base) δ 7.65 (d, 1H, J = 1.8 Hz), 7.58 (s, 1H), 7.42 (d, 1H, J = 8.4 Hz), 7.38 (dd, 1H, J = 1.8, 8.4 Hz), 7.08 (d, 2H, J = 8.1 Hz), 6.79 (d, 2H, J = 8.1 Hz), 3.51 (m, 1H), 3.40 (m, 1H), 3.29 (m, 1H), 3.25 (m, 1H), 2.38 (m, 1H), 2.35 (s, 3H), 2.21 (m, 2H), 1.83 (m, 2H), 1.63(m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.93, 26.37, 35.25, 37.22, 42.12, 53.38, 61.98, 66.04, 125.93, 128.46, 128.60, 129.39, 131.16, 137.48; LCMS (ESI) m/z 465.4 $(M + 1)^+$. The hydrochloride salt had a mp of 164−172 °C; $[\alpha]^{20}_D$ −20.5° (c 0.20, CH_3OH). Anal. ($C_{23}H_{22}Cl_4N_2S\cdot 2.25H_2O$) C, H, N, S.

3β-(4-Chlorophenyl)tropane-2β-*N*-(3,4-dimethoxyphenacyl)carboxamide Ethylene Ketal (7j). Using a procedure similar to that described for **7k**, 1.19 g (0.0043 mol) of **5a** was coupled to 1.02 g (0.0043 mol) of **12h** to give 1.16 g (55%) of **7j** as a white solid: ^{1}H NMR ($CDCl_3$) δ 9.80 (bt, 1H), 7.17 (d, 2H, J = 8.4 Hz), 7.12 (dd, 1H, J = 1.8, 8.4 Hz), 7.05 (d, 2H, J = 8.4 Hz), 7.03 (d, 1H, J = 8.4 Hz), 6.86 (d, 1H, J = 8.4 Hz), 4.10 (m, 2H), 3.95 (m, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 3.63 (dq, 2H), 3.26 (d, 2H), 3.03 (m, 1H), 2.46 (dd, 1H), 2.21 (s, 3H), 2.10 (m, 3H), 1.70 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 129.21, 128.28, 118.43, 110.68, 109.18, 65.02, 64.81, 63.83, 61.31, 55.97, 54.25, 46.24, 41.06, 35.60, 35.16, 26.08, 24.92; LCMS (ESI) m/z 501.8 $(M + 1)^+$.

3β-(4-Chlorophenyl)tropane-2β-*N*-(3,4-dimethoxyphenacyl)carboxthioamide Ethylene Ketal (8j). Using a procedure similar to that described for **8k**, 1.16 g (0.0023 mol) of **7j** was converted to 617 mg (51%) **8j** as a tan solid: ^{1}H NMR ($CDCl_3$) δ 12.20 (bs, 1H), 7.17 (d, 2H, J = 8.4 Hz), 7.08 (dd, 1H, J = 1.8, 8.4 Hz), 7.07 (d, 1H, J = 1.8 Hz), 6.97 (d, 2H, J = 8.4 Hz), 6.90 (d, 1H, J = 8.4 Hz), 4.15 (m, 2H), 3.01 (m, 3H), 3.93 (s, 3H), 3.90 (s, 3H), 3.77 (dd, 1H), 3.44 (d, 1H), 3.28 (m, 1H), 3.19 (m, 1H), 3.10 (m, 1H), 2.21 (s, 3H), 2.10 (m, 3H), 1.71 (m, 2H), 1.56 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 129.83, 128.57, 118.89, 111.27, 109.62, 65.43, 65.36, 65.34, 61.93, 61.26, 56.45, 53.89, 41.27, 36.45, 35.47, 26.57, 25.37; LCMS (ESI) m/z 517.7 $(M + 1)^+$.

3β-(4-Chlorophenyl)-2β-[5-(3,4-dimethoxyphenyl)thiazol-2-yl]tropane (4j) Hydrochloride. Using a procedure similar to that described for **4k**, 620 mg (1.2 mmol) of **8j** was cyclized to give 515 mg (96%) of **4j** free base, which was converted to the hydrochloride salt: ^{1}H NMR ($CDCl_3$, free base) δ 7.50 (s, 1H), 7.15 (dd, 1H, J = 1.8, 8.4 Hz), 7.10 (d, 2H, J = 8.4 Hz), 7.05 (d, 1H, J = 1.8 Hz), 6.86 (d, 1H, J = 8.4 Hz), 6.83 (d, 2H, J = 8.4 Hz), 3.95 (s, 3H), 3.91 (s, 3H), 3.50 (m, 1H), 3.40 (m, 1H), 3.31 (m, 1H), 3.24 (m, 1H), 2.36 (m, 1H), 2.35 (s, 3H), 2.23 (m, 2H), 1.65 (m, 2H), 1.60 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 135.74, 129.50, 128.54, 119.64, 111.99, 110.24, 66.17, 62.02, 56.51, 56.45, 53.35, 42.14, 37.33, 35.49, 26.43, 25.91; LCMS (ESI) m/z 455.6 $(M + 1)^+$. The hydrochloride salt had a mp of 159−168 °C; $[\alpha]^{20}_D$ −9.0° (c 0.20, CH_3OH). Anal. ($C_{25}H_{28.5}Cl_{2.5}N_2O_2S\cdot 1.75H_2O$) C, H, N, S.

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Supporting Information Available: Elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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